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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/032,361	12/21/2001	Kevin McGrath	1443.025US1	5006

21186 7590 09/03/2004

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EXAMINER	
LIU, SAMUEL W	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 09/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/032,361	MCGRATH, KEVIN	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) *30-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1-21-03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

Claims 1-42 are pending.

Applicant's request (filed 26 July 2004) for extension of time of one month has been entered.

Election/restriction

Applicants' election of Group I, claim 1-29 with traverse in the response filed 26 July 2004 28 is acknowledged. The Traversal is on the ground(s) that search all the claims would not place serious burden on the Examiner (see page 1 of the response).

The applicants' argument is found unpersuasive because examining all the groups (all the claims) would require additional search of a process of inhibiting ubiquitination of hypoxia-inducible factor 1 alpha (HIP 1-α) in a mammalian cell (e.g., human cell) under classes 514 and 435 if Group II were included, and require search of activation of vascular endothelial growth factor (VEGF) due to inhibitory mode of DNA-binding protein, i.e., HIP 1-α, in the said cell.

Thus, co-examination of each Groups I and II would be a serious burden of search. Therefore, the elected claims 1-29 are examined in this Office action. Claims 30-42 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

IDS

The references cited in the IDS filed 21 January 2003 and the IDS filed 6 November 2003 have been considered by Examiner.

Specification/Claim/ Objections

The disclosure is objected to because of the following informalities:

In the page before page 1 (*note the actual first page of specification is not labeled*), line 2, "EPO" and VEGF" should be spelled out in full for the first instance of use. See also page 1, line 12, "DFX".

In page 8, lines 17-18, "Hyp" in the peptide sequences of SEQ ID NOs: 4 and 5, should be clarified or should indicate "Hydroxyproline" because of the first instance of use in the specification, "Hyp" should be spelled out in full.

In page 23, line 25, "0-15% wt" should be changed to "0-15 wt%" for the consistency (see line 24, "0-3 wt%" *etc.*).

In page 25, line 30, after the peptide sequence, "YGR ... "FGL", "(SEQ ID NO:7)" should be added.

In claim 11, "VEGF" should be spelled out in full at first recitation in the claim.

Appropriate correction is required.

Claim Rejection under 35 USC 101

35 U.S.C. §101 states:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-18 are rejected under 35 USC 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1, 2-3, 11 and/or the dependent claims thereto, as written, do not sufficiently distinguish over polypeptides as they exist naturally because the claims do

not particularly point out any non-naturally occurring differences between the claimed polypeptide and the naturally occurring polypeptides. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" or "Purified". See MPEP 2105.

Claim Rejections - 35 USC § 112, the second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 3-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 recitation "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d). See also claims 11 and 19. The dependent claims are also rejected.

Claim 5 is awkward because the claim recites "t-butyalanine" twice. See also claims 13 and 21.

Claim 9 is indefinite because the claim recitation "at least 90% identity to SEQ ID NO:4" does not make sense. Note that the SEQ ID NO:4 peptide consists of only 8 amino acid residues; and thus, the minimal % of structural alteration would be one residue change, i.e., 87.5%.

Claim 27 is indefinite because the recitation "...a wound dressing" *per se* is not a pharmaceutical formulation. Insertion of the word "in" between "is" and "a" would overcome the rejection.

Claim 29 is indefinite because the recitation "...a surgical implant" *per se* is not a pharmaceutical formulation. Insertion of the word "used in" between "is" and "a" would overcome the rejection.

Claim Rejections - 35 USC § 112, the first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification fails to describe the polypeptide variant that has 90% sequence identity (subsequences) to the full-length polypeptide of SEQ ID NO:7 (claim 1), and that the variant has an activity. These subsequences represent polypeptide variants comprising deletion/truncation, substitution, addition and/or insertion mutations. Note that, for SEQ ID NO:7, 10% amino acid alteration counts for at least three amino acid mutations). The current disclosure fails to provide a representative number of the variants (e.g., ~ 10% amino acid variations, any substitutions, deletions or /and insertions) that retain the activity of full-length polypeptide SEQ ID NO: 7. Applicants were thus not in a

possession of the claimed variant polypeptides. Therefore, the specification lacks written description of the claimed polypeptide.

Applicants may wish to amend the claims to additionally list a specific and measurable activity or function that these variables must have so that one skilled in the art can recognize when they are in possession of a polypeptide having at least 90% identity to SEQ ID NO: 7 and having a specific function, for example.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 3-8 and 11-16 are rejected under 35 U.S.C. 102 (a) as being anticipated by Jaakkola et al. (*Science* (April 2001) 292, 468-472).

Jaakkola et. al. teach an inhibitor of HIF-1α ubiquitination comprising the sequence consisting of "DLDLEMLAP*YIPMD" (see "HIP-1α (5556-674) sequence depicted in Figure 3) wherein the 9th residue (i.e., proline 564) is hydroxylated, which anticipates the instant claim 3.

Jaakkola et al. teach that acidic residue of said peptide is aspartic acid, as applied to the instant claim 4.

Jaakkola et al. teach that aliphatic residue of said peptide is alanine and/or leucine, as applied to the instant claims5.

Jaakkola et al. teach that polar residue of said peptide is proline, and/or, as applied to the instant claim 6.

Jaakkola et al. teach that apolar residue of said peptide is methionine, and/or proline, as applied to the instant claim 7.

Jaakkola et al. teach that aromatic residue of said peptide is tyrosine, as applied to the instant claim 8.

Also, Jaakkola et al. teachings are applied to the instant claims 11-16 because the composition of claims 11-16 is identical to that of claim 3-8 and because transcriptional activation of vascular endothelial growth factor (VEGF) by the above-stated composition in hypoxia-inducible pathway is an intrinsic property of the said composition, and because the structure of said composition will not be altered due to its use in activating VEGF, for example. Thus, Jaakkola et al. anticipate claims 3-8 and 11-16 of the current application.

Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3-10, 11-16, 19-24 and 27-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over McKnight S. I. et al. (US Pat. No.6566088) and taken with Jyu, F. et al. (*Proc. Natl. Acad. Sci. USA* (August 2001) 98, 9630-9635), and Jones A. et al. (*Clin. Cancer Res.* (May 2001) 7, 1263-1272).

McKnight et al. teach a polypeptide which acts as a enzymatic substrate for a hypoxia-inducible factor (HIF)-specific prolyl hydroxylase wherein the peptide has a consensus motif of "LAPY" (see the patent claims 1-4 and column 3, lines 39-41) and

wherein said polypeptide is human HIF-1α (see column 3, lines 32-34). A segment of the human HIF-1α comprising "LAPY" is "LAPYIPMD" which reads on Formula II of claim 3. Thus, the McKnight et al. teaching is applied to the instant claims 3 and 11.

McKnight et al. teach that acidic residue of said peptide is asp artic acid, as applied to the instant claims 4 and 12.

McKnight et al. teach that aliphatic residue of said peptide is alanine and/or leucine, as applied to the instant claims 5 and 13.

McKnight et al. teach that polar residue of said peptide is proline, as applied to the instant claims 6 and 14.

McKnight et al. teach that apolar residue of said peptide is methionine, and/or proline, as applied to the instant claims 7 and 15.

McKnight et al. teach that aromatic residue of said peptide is tyrosine, as applied to the instant claims 8 and 16.

Also, McKnight et al. teach a composition comprising a peptidic substrate which is the above-mentioned peptide (see column 4, lines 21-29), and teach that the said composition (i.e., the identified agent) is used as a pharmaceutical composition (see column 2, lines 55-57), wherein the composition additionally comprises salts and buffers (see column 3, lines 47-58). The McKnight et al. teaching is thus applied to the instant claims 19-24 and 27-29. Please note that the intended use of the claimed composition (e.g., claim 2 recites "the pharmaceutical composition of claim 19 that is (*used for*) a wound dressing") has no patentable weight because the said composition (the formulation) will not be altered due to use of the composition for the wound dressing condition.

McKnight et al. do not expressly teach the sequence which meets all the limitation set forth in claim 3 formula II.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare the claimed polypeptide *because* the McKnight' s patent has disclosed that the LAPYI motif is essential for proline hydroxylation, and teach that proline hydroxylation occurs at proline residue 564 of the human HIF-1α (see column 3, lines 32-34), and *because* Yu et al. teach that protein hydroxylation occurring at proline 564 in the sequence of residues 549-575 (see Figure 2, panel A); this is because mutation of proline 564 abolishes interaction between wild-type HIF-1α and *von Hippel Lindau tumor suppressor protein* (VHL), wherein the VHL protein mediates ubiquitination of the HIF-1α protein (see abstract and page 9630). Thus, in combination of the McKnight et al. teaching with the Yu et al. teaching, the skilled artisan would have made an inhibitor of HIF-1α ubiquitination comprising a peptide having the sequence as characterized in Formula II and successfully arrive at the current invention (claims 3-10, 19-24 and 27-29).

Since the HIF-1α protein up-regulates (activates) vascular endothelial growth factor (VEGF) hypoxia-inducible pathway, as taught by Jones A. et al. reference (see abstract and page 1270), the above McKnight's composition is applicable to the current application (claims 11-16). The skilled artisan would thus have prepared an activator of VEGF transcription comprising the McKnight's composition and readily arrived at the current invention.

Therefore, the claimed invention would have been *prima facie* obvious at the time it was made.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is 571-272-0949. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

SWL

Samuel Wei Liu, Ph.D.
Art Unit 1653, Examiner
August 24, 2004

ROBERT A. WAX
PRIMARY EXAMINER